

Remarks

Claim 8 is amended, and withdrawn claims 9-50 are canceled. New claims 54-63 are added. Claims 1, 4, 7, 8, and 54-63 are now pending. The amendment to the claim and the new claims are supported by the specification as filed, and no new matter has been added.

New claims 54-63 are supported by the specification as filed, for example, at page 37, lines 12-24, page 38, lines 8-13, page 71, lines 13-22, and at page 76, lines 6-11.

I. The 35 U.S.C. §112, Second Paragraph Rejection of Claim 8

In the Final Office Action mailed November 16, 2004 (hereinafter the Final Office Action), the Examiner rejected claim 8 under 35 U.S.C. §112, second paragraph, alleging that claim 8 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant submits that claim 8 has been amended so as to obviate this rejection. Applicant respectfully requests that the Examiner withdraw the rejection of claim 8 under 35 U.S.C. § 112, second paragraph.

II. The 35 U.S.C. §112, First Paragraph Rejection of Claims 1 and 8

The Examiner rejected claims 1 and 8, alleging that those claims are unpatentable under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement by containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Claim 1 recites a modified fibronectin type III (Fn3) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue. Claim 8 depends from claim 1 and recites that Asp 7, Asp 23, and Glu 9 have been substituted with at least one other amino acid residue.

Applicant asserts that the specification as originally filed provides an adequate written description of the claimed invention. Applicant may show adequate written description by demonstrating that an invention is complete by disclosure of sufficiently detailed, relevant

identifying characteristics that provide evidence that Applicant was in possession of the claimed invention, *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem. v. Gen-Probe Inc.*, 323 F.3d 956, 963, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.3d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Furthermore, the written description requirement states that the Applicant must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. *Capon v. Eshhar v. Dudas*, 2005 U.S. App. LEXIS 16865 (Fed. Cir. 2005). Moreover, it is not necessary that every permutation within a generally operable invention be effective in order to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *Capon v. Eshhar v. Dudas*, 2005 U.S. App. LEXIS 16865 (Fed. Cir. 2005).

Applicant provides structural characteristics of the claimed Fn3 molecule. For example, the structure of wild-type Fn3 molecules are known (*see, e.g.*, Main *et al.* 1992, of record, and page 18, line 14, through page 20, line 5 of the specification). The claimed modified Fn3 molecule has a mutation of the Fn3 structure, *i.e.*, a substitution of at least one of Asp 7, Asp 23 or Glu 9. As such, Applicant has recited specific structural modifications to the Fn3 molecule. Thus, Applicant provides the art worker with structural characteristics of the claimed modified Fn3 molecule.

Applicant also provides functional characteristics of the claimed modified Fn3 molecule, namely, that the modified Fn3 molecule comprises a mutation that is a stabilizing mutation. A stabilizing mutation is defined in the specification at page 6, lines 20-24, as “a modification or change in the amino acid sequence of the Fn3 molecule, such as a substitution of one amino acid for another, that increases the melting point of the molecule by more than 0.1°C as compared to a molecule that is identical except for the change.” Applicant provides a method for determining the melting point of the molecules in Example 19, which begins at page 63 of the specification. Thus, Applicant provides the art worker with functional characteristics of the claimed modified Fn3 molecule.

Applicant respectfully asserts that sufficient detail of the identifying structural and functional characteristics of the modified Fn3 molecule have been provided or were available to one of ordinary skill in the art at the time the application was filed, and as such, Applicant was in possession of the full scope of the claimed invention at the time the application was filed.

At page 3, lines 11-12 of the Final Office Action, the Examiner alleges that Applicant has not provided the art worker with a defined structure for the type of Fn3 structure in its native or modified state. As detailed hereinabove, Applicant respectfully submits that the specification, in combination to what was known in the art at the time the application was filed, provides the art worker with sufficient structural and functional characteristics of the modified Fn3 molecule so as to satisfy the requirements of 35 U.S.C. §112, first paragraph.

At page 3, lines 5-8 of the Final Office Action, the Examiner alleges that the specification does not provide an adequate written description of the amino acid residues that can be substituted for at least one of Asp 7, Asp 23, or Glu 9 of the Fn3 molecule. At lines 8-11 of page 3, the Examiner further alleges that the "another amino acid residue" can read on any kind of natural and/or synthetic amino acids, singly or in combinations, for the different recited positions of the Fn3 molecule. And at page 5, lines 18-21, the Examiner concludes that "at the time of applicant's invention, applicants appear not to be in possession of the huge scope of any amino acid residue replacing any of the three recited positions in any type of Fn structure." Applicant respectfully submits that since the claims recite that the modified Fn3 molecule comprises a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue, each of Asp 7, Asp 23 and/or Glu 9 may individually be substituted with a single amino acid residue. Applicant also submits that the art worker is well apprised of potential amino acid residues to consider for substitution. For example, Tables 3 and 4 of Chapter 2400 of the MPEP provide the art worker with some amino acids (Table 3) and modified or unusual amino acids (Table 4) that could be considered for substitution for at least one of Asp 7, Asp 23 or Glu 9 in the Fn3 molecule. In particular, Applicant asserts that once he determined that residues Asp 7, Asp 23 and Glu 9 of the Fn3 molecule were the amino acids contributing to unfavorable intra-molecular electrostatic interactions, one of ordinary skill in the art would know or be able to determine which amino acid residues would likely be able to be substituted to enhance the stability of the Fn3. For example, Applicant submits that one of skill in the art would know that since both Asp

and Glu have negative charges, the introduction of an amino acid that has either a neutral or positive charge would likely reduce or remove the unfavorable electrostatic interaction from residues 7, 23 and/or 9 and would thus provide a likely candidate for substitution. Applicant has provided the art worker evidence of this as a substitution of Asp 7 with a neutral (*e.g.*, Asn) or positively-charged (*e.g.*, Lys) amino acid reduces the unfavorable interactions (page 75, lines 6-8 of the specification). And even if, for the sake of argument, the art worker lacked guidance as to which amino acid residue to select for substitution, the scope of the claims is described functionally as the substitution is recited to stabilize the molecule. As such, the art worker would need only to test the substitution(s) at the recited position(s) to determine whether the substitution stabilized the molecule using, *e.g.*, the assay described in Example 19, which begins at page 63 of the specification, testing which Applicant submits is not undue.

At pages 3-4 of the Final Office Action, the Examiner cites to page 76 of the specification to support the proposition that an electrostatic interaction can present an unpredictable effect in the Fn3 molecule. Regarding the passage at page 76, lines 19-20 of the specification (“Therefore, it is not clear why these destabilizing residues are almost completely conserved in FNfn10.”), Applicant submits that it is evident from the context of the sentence that the passage refers to the general lack of understanding as to why in nature the Asp 7, Asp 23 and Glu 9 triad has not evolved into a more stable state. The Examiner appears to be interpreting this passage as meaning that the electrostatic effect of the interactions of the residues is unpredictable. To the contrary, the electrostatic interactions of specific residues provide a place for one of skill to modify the proteins to make them more stable, once a researcher determines which residues to investigate in a molecule.

The Examiner states at line 8, page 4 of the Final Office Action that there are just too numerous factors, variables and/or mechanisms necessary to identify the destabilizing regions for each kind of fibronectin (Fn) in each species. However, Applicant determined that three specific residues (*i.e.*, Asp 7, Asp 23 and Glu 9) of the Fn3 molecule are the amino acids that contribute to unfavorable intra-molecular electrostatic interaction in the Fn3 molecule. Applicant respectfully submits that the claim scope reflects this, *i.e.*, claim 1 is directed to a modified Fn3 molecule comprising a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue. Accordingly, Applicant respectfully asserts that it is not necessary for the art

worker to identify the destabilizing regions for each kind of fibronectin in each species as the scope of the claims reflects that Applicant has identified three specific residues in a Fn3 molecule thereby providing very specific structural characteristics to the art worker.

Regarding the Dao-pin document, Applicant cited this document for the proposition that substitutions of positively charged residues for other residues do not necessarily have a stabilizing effect on a protein. One of skill in the art, having read Dao-pin, would understand that in certain circumstances the substitution of an attractive electrostatic interaction would have a small effect on stability. It should be noted that Dao-pin was attempting to introduce a potentially favorable interaction, rather than eliminating an existing unfavorable electrostatic interaction.

Thus, Applicant has provided structural characteristics of the claimed modified Fn3 molecule as the structure of wild-type Fn3 molecules were known to the art worker at the time the application was filed. Applicant has recited specific structural modifications to the known Fn3 molecule, *i.e.*, the modified Fn3 molecule has a substitution of at least one of Asp 7, Asp 23 or Glu 9. Applicant has also recited functional characteristics of the claimed modified Fn3 molecule, namely, that the modified Fn3 molecule comprises a stabilizing mutation, which mutation is functionally described in the specification together with an assay to measure the functional characteristic. Applicant has further provided examples of stabilizing mutations of the recited amino acids. Thus, it is respectfully asserted that the Applicant has provided adequate written description of the claimed modified Fn3 molecule as Applicant has disclosed in sufficient detail the relevant identifying structural and functional characteristics that provide evidence that the Applicant was in possession of the full scope of the claimed invention at the time the application was filed. Thus, Applicant submits that claims 1 and 8 satisfy the written description requirements of 35 U.S.C. § 112, first paragraph.

In view of the above, Applicant respectfully requests withdrawal of the rejection of claims 1 and 8 under 35 U.S.C. § 112, first paragraph.

III. Allowable Subject Matter

Applicant acknowledges that claims 4 and 7 are objected to as being dependent upon a rejected base claim but would be allowable if rewritten in independent form.

If necessary, please charge any additional fees or credit overpayment to Deposit Account 50-3503.

Respectfully submitted,

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CERTIFICATE UNDER 37 C.F.R. 1.8: The undersigned certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 21st day of September 2005.

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